REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

Withdrawal of the several previous rejections is noted with appreciation. Claims 1-46 are in the case and are before the Examiner.

A. Rejection Under 35 USC §112, First Paragraph

All of the claims were newly rejected under the first paragraph of Section 112 as allegedly failing the description requirement and the enablement requirement. This basis for rejection cannot be agreed with and is respectfully traversed as discussed below.

The Action asserts that the phrase "said chimer molecule containing up to about 5 percent conservatively substituted amino acid residues in the HBc sequence relative to SEQ ID NO:1" amended in to claims 1, 11 and 25 is new matter. The basis for this rejection is understood to be because the complete quoted phrase is not present in a single sentence in the specification. The Action states that although

> the conservatively substitution of amino acids of epitops (sic) and native cystines is described in paragraphs [0081], [0231 and [0393] of the specification, no description of "5 percent conservatively substituted amino acid residues in the HBC sequence relative to SEQ ID NO:1" is found in the specification.

As was pointed out in the previous amendment, the specification at paragraph [0080] should also be consulted. Still further, the Examiner's attention is invited to paragraph [0231] that states that

> [0231] In addition to the before-discussed N- and C-truncations, insertion of various epitopes and spacers, a contemplated chimer molecule can also contain conservative substitutions in the amino acid residues that constitute HBc Domains I, II, III and IV. Conservative substitutions are as defined before. [Emphasis supplied.]

It is thus submitted that the specification teaches that the residues that constitute Domains I, II, III and IV can themselves be conservatively substituted.

The next paragraph [0232] teaches that the preferred HBc sequence is that of SEQ ID NO:1. Thus,

> [0232] . . . The HBc portion of a chimer molecule of the present invention; i.e., the portion having the HBc sequence that has other than a sequence or residue of an added immunogen, anti-antigen, linker, flexible linker arm or heterologous residue(s) that are a restriction enzyme artifact, most preferably has the amino acid residue sequence of subtype ayw that is shown in FIG. 1 (SEQ ID NO: 1), less any portion or portions of the subtype ayw sequence that are absent because of truncation at one or both termini.

The following paragraph, [0233], completes the thought by teaching which sequence is used as a reference for substitution {SEQ ID NO:1}, and preferred percentages of substitution (20%, 10%, 5% and 3%), the penultimate percentage of which is recited in the rejected claims.

> [0233] When the HBc portion of a chimer molecule of the present invention as above described has other than a sequence of a mammalian HBc molecule corresponding to positions 2 through about 183, up to about 20 percent of the amino acid residues are substituted as compared to SEQ ID NO: 1 from position 2 through 183, and preferably position 2 through 163. It is preferred that up to about 10 percent, and more preferably up to about 5 percent, and most preferably up to about 3 percent of the amino acid residues are substituted as compared to SEQ ID NO: 1 from position 2 through 163.

It is submitted that although the quoted and objected to phrase is not recited in a single sentence in the specification, "the claimed subject matter need not be described in *heac verba* in the specification in order for that specification to satisfy the description requirement." *In re Wright*, 9 USPQ2d 1649, 1651 (Fed. Cir. 1989) citing *In re Smith*, 178 USPQ 620, 624 (CCPA 1973). Rather, the important point for the description requirement is that the application provide evidence "to those skilled in the art that applicant had invented the subject matter later claimed." *In re Wilder*, 222 USPQ 369, 372 (Fed. Cir. 1984) citing *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983). It is submitted that the disclosures cited above in contiguous paragraphs [0231-0233] provide the required evidence that the inventors had the invention now claimed as of the filing date and that no new matter has been added. It is thus submitted that this basis for rejection should be withdrawn.

B. Rejections Under 35 USC §103

1. First Rejection

Claims 1-6, 8-14, 16-22, 30-42 and 46 have been rejected as allegedly being obvious from the combined

disclosures of Pumpens 1995, in view of Zlotnick (1997) and Zheng (1992). This rejection is respectfully traversed.

The Action notes that the Pumpens 1995 disclosure teaches chimeric proteins that contain added epitope-containing sequences, and particles self-assembled from them. The Action acknowledges that Pumpens does not teach replacing one or both cysteine residues at positions 48 and 107 with another residue and adding a further cysteine near the C-terminus to gain stability.

Zlotnick teaches C-truncated HBc sequences in which the Cys residues at positions 48, 61 and 107 have been replaced and a C-terminal Cys added (Cp*150) or not (Cp*149). However, Zlotnick teaches the presence of no added sequence at the N-terminus, the C-terminus nor in the loop. The Action notes that the results reported by Zlotnick suggest that the presence of the C-terminal cysteine in Cp*150 that is absent in Cp*149 leads to disulfide bond formation that can promote capsid assembly. Moreover, in both of the examples in Zlotnick [Fig. 1(a) of Zlotnick] when Cys residues at positions 48 and 107 are replaced, the Cys at position 61 is *also* replaced. Thus, Zlotnick provides no incentive to replace one or both cysteine residues at positions 48 and 107 with another residue, but still retain the cysteine at residue position 61, as required by the present claims.

The Zheng paper is said to teach the role the HBc native cysteines play in particle formation. Zheng teaches that the native Cys 107 is buried within the particle structure and is not involved in capsid formation, whereas Cys 61 and Cys 183 are always involved in capsid formation and Cys 48 is sometimes so involved. Zheng also contains no teaching concerning the effect of the presence of an added sequence at the N-terminus,

the C-terminus or in the loop. Zheng is silent as to such chimers.

Taking all of these teachings together, the Action asserts that it would have been obvious to a worker of ordinary skill to pick and choose among the disclosures to come up with a chimer having a C-terminal truncation with an inserted sequence from Pumpens that was stabilized by the internal cysteine-free native sequence of Zlotnick and gain further stability by deleting one or both of two specific cysteine residues as taught by Zheng to be involved in particle formation. These selections were to be made with none of Ruschig's blaze marks on the trees in the prior art forest to motivate that skilled worker to make those specific changes. [In *re Ruschig*, 154 USPQ 118, 122 (CCPA 1967).]

It is further submitted that rather than aiding the argument for obviousness, the Zheng disclosure actually teaches away from the present invention. More particularly, as noted from the title and claim language, the present invention is directed to stabilized HBc chimer particles. The asserted thrust of the relied-on Zlotnick article is that a C-terminal Cys residue helps stabilize the HBc particles therein disclosed that *inter alia* have all of their native Cys residues replaced. Zheng teaches that the Cys 48 residue imparts some HBc interchain disulfide bond formation and thereby presumed enhanced stability. Thus, one would expect from reading both disclosures that the presence of the Cys at position 48 would enhance stability.

The present claims and the disclosure are directed to particles that are more stable when one or both of the Cys residues at positions 48 and/or 107 are ABSENT. The

specification at paragraph [0527] of the published application or page 192 states:

> [o]f particular note was the fact that the C-terminally stabilized C48S/C107S chimer appeared to be entirely disulfide bonded at day zero, whereas its C48/C107 counterpart was not and did not reach the same level of cross-linking achieved by the C48S/C107S chimers during the period of study. Additionally, the engineered particle HBc149(C48S/C107S)W62C/F97C+C exhibited the same high level of cross-linking at day zero.

It is submitted that one would not expect particles lacking one or both possible interchain disulfide bond formers to be more stable than a similar particles containing one or both extra possible disulfide bond formers as is disclosed.

The Examiner's attention on this point is also invited to Figs. 4E-4H. The first two figures illustrate size exclusion chromatographs of particles containing a C-terminal Cys and the native Cys residues at positions 48 and 107 on days zero and 14 after their preparation. The small peak at just past 15 mL is noted in Fig. 4F that shows a small amount of dimer being present. No such dimer peak is seen in either of Fig. 4G or Fig. 4H that illustrate a similar assay for similar particles in which both of the native Cys residues at position s48 and 107 were replaced with Ser residues.

It is submitted that those results were intuitively unexpected and even more unexpected from the reading of Zheng in conjunction with Zlotnick. It is thus submitted that this basis for rejection should be withdrawn.

2. Second Rejection

Claims 1-6, 8-28 and 30-46 have been rejected as allegedly being obvious from the combined disclosures of Page et al. (WO 01/98333 A2) and Birkett (US 6,231,864) both in view of Zheng (1992). This rejection is respectfully traversed.

The Page disclosure used here is similar to that of the Pumpens article with the inclusion of a C-terminal Cys residue. The Action notes that Page does not teach the presence of a heterologous linker in the HBc loop, but that teaching is found in Birkett. Zheng is used in the Action in the rejection discussed above.

The response to the previous rejection under 35 USC §103 is repeated here by reference. It is submitted that the deficiency of Zheng alone is no different from the deficiencies of the disclosures of Zheng plus those of Zlotnick that were discussed previously. Zheng provides a suggestion of enhanced stability because of the presence of one or both Cys residues at positions 48 and 107, and the inventors here found that the particles formed are more stable without those presumably stabilizing residues. That claimed result is unexpected, and that claimed result is patentable. It is submitted that this rejection should be withdrawn.

C. Summary

Each of the bases for rejection has been dealt with and overcome or otherwise made moot.

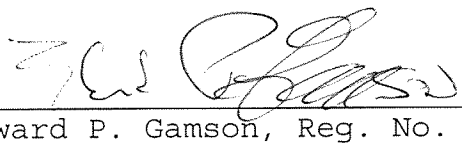
It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please

charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By 
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